Correlation between magnetic resonance imaging and ultrasound measurements of eye muscle thickness in thyroid-associated orbitopathy

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Aims. To compare ultrasound (US) and magnetic resonance imaging (MRI) measurements of horizontal eye muscle thickness in patients with thyroid-associated orbitopathy (TAO) and to compare these measurements according to the phase of the disease, the severity of exophthalmos, and the experience of the investigator.
Methods. A total of 180 orbits of adult patients with TAO were investigated from May 2007 to December 2012. In addition to their general ophthalmic examination, all patients underwent ultrasonographic measurement of horizontal eye muscle thickness with the B-scan technique and MRI examination of the orbit. Correlations between values obtained by US and MRI were determined for different subgroups according to disease activity (active, inactive), exophthalmos values (Hertel < 18 mm; Hertel 18-22 mm; Hertel > 22 mm), and the time period of examination (2007-2009; 2010-2012).
Results. Positive moderate correlation between US and MRI values for the medial rectus muscle (MRM; r = 0.690) and for the lateral rectus muscle (LRM; r = 0.572) was found. Significantly higher correlation was found for the MRM ($P < 0.0001$) and the LRM ($P = 0.0008$) in the time period 2010-2012 than in that of 2007-2009. Increasing correlation was found for MRM with increasing values of exophthalmos but this increase was not statistically significant. In the active phase of the disease compared to the inactive phase, statistically significant increased correlation ($P = 0.019$) was found for the LRM.
Conclusions. Ultrasonographic measurement of horizontal eye muscles thickness in TAO moderately correlates with values obtained using MRI. The accuracy of ultrasonographic measurements in particular increases with the experience of the investigator.

Key words: thyroid-associated orbitopathy, orbit, ultrasound, magnetic resonance imaging, extraocular muscles

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INTRODUCTION

Thyroid-associated orbitopathy (TAO), also known as thyroid eye disease, Graves' ophthalmopathy, and Graves' orbitopathy, is an autoimmune inflammatory disorder of the orbit. It is closely associated with Graves' disease, a form of hyperthyroidism in which autoantibodies stimulate the thyrotropin receptor. As much as 50% of patients with Graves' disease will develop orbital changes[1-5], even though activity is clinically detected in only a few cases[2,3,6]. The diagnosis of hyperthyroidism and TAO usually occurs within 18 months of each other[7]. Women are affected about 10 times more often than men[7]. Relatively rarely, in up to 10% of the time, TAO can also occur in euthyroid and hypothyroid patients[4,5].

The symptoms and signs of TAO vary. The most common symptoms are change in appearance, excess tearing, light sensitivity, eye pain, and double vision[8]. Signs range from upper eyelid retraction, periorbital swelling and redness, conjunctival injection and swelling to proptosis (exophthalmos) and incomplete lid closure (lagophthalmos) with exposure keratopathy and restriction of ocular excursions in one or more directions of gaze[8]. The natural course of the disease shows an initial active inflammatory phase followed by a static fibrotic phase. The exact rate and duration of disease phases can vary and sometimes be unpredictable[4]. The distinction between the two phases is important. Immunosuppression and orbital radiotherapy are more effective in the active phase[1,6]. On the other hand, strabismus surgery should be performed in the fibrotic inactive phase when extraocular muscles are scarred[9]. Because TAO patients must be followed and treated on the basis of disease severity and activity, several different classification systems based on the clinical assessment have been developed (NOSPECS-score and Clinical Activity Score) (ref.[10,11]).

Accurate and reproducible imaging techniques of the orbit that allow visualization of the orbit content and evaluation of extraocular muscles, and help to exclude other clinical entities are very important for the diagnosis and successful management of TAO. Advantages and disadvantages of different radiological modalities in

TAO have been discussed in several published reviews[12,13]. Ultrasound (US) is a non-invasive, well-established, and widely used imaging modality that enables differential diagnosis of proptosis, evaluation and measurement of extraocular muscles, assessment of the optic nerve, and detection of the existing inflammation[14-19]. Its disadvantage is low interobserver reproducibility[14]. Computed tomography (CT) is a quick and widely available imaging technique for orbital anatomical structures. It shows muscle thickness and helps to diagnose compressive optical neuropathy. Limitations are poor information about the activity of TAO and radiation exposure[1,13]. MRI gives a better resolution of orbital soft tissue than CT, adds information regarding disease activity, and is free of any radiation burden[20-24]. However, it is more expensive and lengthy in comparison to CT, and it is not widely available. But in the majority of cases, when clear clinical signs and symptoms of TAO and laboratory evidence of thyroid disease are present, CT or MRI is not required.

Up to the present, only few studies have compared US and MRI regarding the measurement accuracy of eye muscle thickness in patients with TAO (ref.[24-26]), and mostly only poor correlation was found. The aim of the present study was to compare the correlation of US and MRI measurements of maximal horizontal eye muscle thickness in patients with TAO according to the phase of the disease, the severity of exophthalmos and the experience of the investigator.

MATERIAL AND METHODS

Subjects

A total of 180 orbits of 77 adult patients with TAO were investigated (eleven patients were examined twice and one patient was examined three times during the study period). The study group included 53 females and 24 males, age range 18-81 years, median age 49.0. All patients had recent laboratory evidence of thyroid disease and clinical signs and symptoms of TAO. Enrollments of patients were carried out consecutively between May 2007 and December 2012. Clinical assessment included a full ophthalmic examination: visual acuity, intraocular pressure measurement, evaluation of the adnexa and eyelids, slit-lamp evaluation of the anterior segment, and fundus evaluation by indirect ophthalmoscopy. Eye motility was also evaluated. Proptosis was measured by Hertel exophthalmometer. All patients were asked about symptoms. The Clinical Activity Score (CAS) was determined according to the clinical findings.

The study protocol was approved by the local Ethics Committee and the study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki.

Ultrasound examination and measurement of horizontal muscle thickness

All patients were examined with B-scan ultrasound (Compuscan, Storz, USA), the frequency used was 10 MHz, and the device was set at 70-73 dB. The examination was performed in the supine position through closed lids. The patients were asked to look straight ahead, so that the eye was held in the primary gaze position. This eye position was checked using axial topographic scans before measurements. The order of examination of the muscles was medial rectus followed by lateral rectus. Both orbits were examined in the same way. The largest diameters of the horizontal extraocular muscles were measured according to the generally recommended protocol[28]. The probe was placed in the region of the equator of the eye opposite to the muscle to be measured (on the lateral side when examining the medial rectus muscle, and on the nasal side when examining the lateral rectus muscle). Each muscle was scanned from its anterior part along the muscle belly posteriorly. After the muscle was identified (a stripe with lower acoustic reflectivity than the surrounding orbital tissue), a suitable section was frozen on the screen and the measurement was taken at the point of the greatest enlargement of the muscle, perpendicular to the muscle axis, using calipers. The measurement of the vertical rectus muscles was performed only occasionally. All ophthalmic examinations and ultrasound measurements were performed by the same investigator, one of the authors (MK), independently of the MRI examinations and measurements. The data obtained were recorded and saved.

MRI examination and measurement of horizontal muscle thickness

MRI examination of the orbit was performed after US no later than 10 days from the ultrasound examination. The MRI device used in this study was Magnetom Avanto 1.5 T (Siemens, Erlangen, Germany) with a CP head array coil. The sequences used were: T1-weighted inversion recovery in the transverse plane (0.9 mm slice thickness), T2-weighted turbo spin echo in the coronal plane (3 mm slice thickness), T2-weighted 3D sequence in the coronal plane (0.7 mm slice thickness), and T2-weighted spin echo with 16 echoes in the coronal plane (3 mm slice thickness). All sequences covered the entire area of both orbits. No contrast material was used. Images were stored in picture archiving and communication system (PACS) (IMPAX version 6.4, Agfa HealthCare, Mortsel, Belgium). Measurement of thickness of intraorbital muscles was performed by one radiologist, one of the authors (RK), during three weeks after the completion of patient enrollment. All MRI measurements were performed independently of the US examinations. Measurements of the extraocular muscles were performed on multiplanar reconstructions in T1-weighted inversion recovery sequence using an evaluating PACS station. The largest horizontal diameter for the medial and lateral rectus muscles was measured on the reconstruction in the plane perpendicular to the course of the long axis of the orbit.

Statistical analysis

Statistical data analysis was performed for the entire study group first. Correlation between values obtained by US and MRI measurements of horizontal recti muscles was determined. After this basic analysis, the data were divided into different subgroups according to disease activity (active TAO with CAS ≥ 1 when immunosuppressive treatment was necessary and inactive TAO with CAS = 0 with no immunosuppressive medication and with a stable ocular finding for at least six months), exophthalmos values (Hertel < 18 mm; Hertel 18-22 mm; Hertel > 22 mm), and time period of the examination (2007-2009; 2010-2012). Correlation of US and MRI values of horizontal recti muscles in each group was investigated and compared.

Data were analyzed using SPSS version 15 (SPSS Inc., Chicago, USA) and Statistica version 10 (StatSoft Inc., USA). The normality of data was assessed using the Kolmogorov-Smirnov test. Spearman correlation analysis was used to determine the correlations between US and MRI values. The T-test for equality of correlation coefficients was used to compare two correlation coefficients. Statistical significance was set at 5%.

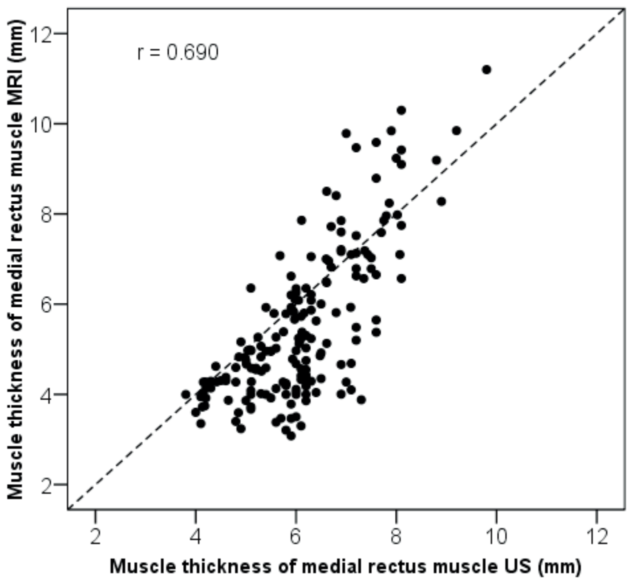

Fig. 1. Spearman correlation between ultrasound (US) and MRI for the medial rectus muscle (r = correlation coefficient).

RESULTS

The median and (1st to 3rd) quartiles of the largest diameter of the medial and lateral rectus muscles measured by ultrasound were 6.06 (5.30-6.90) mm and 4.50 (4.10-5.10) mm, respectively, and on MRI scans 5.50 (4.27-6.57) mm and 4.01 (3.45-4.96) mm, respectively. For more details, see Table 1. Median values of the largest diameter of horizontal extraocular muscles in different subgroups are given in Table 2.

A positive moderate correlation between US and MRI values was found in the entire study group. The correlation coefficient for the medial rectus muscle (MRM) was r = 0.690 (Fig. 1) and for the lateral rectus muscle (LRM) r = 0.572 (Fig. 2). Correlation coefficients in the subgroup of patients with active TAO were r = 0.712 for the MRM and r = 0.678 for the LRM, and in the subgroup with inactive TAO r = 0.662 for the MRM and r = 0.433 for the LRM. Although correlation coefficients were higher in the active phase of TAO, a statistically significant increased correlation (P = 0.019) was found only for LRM in the active phase of the disease compared to the inactive phase. Increasing correlations were also found for the MRM with increasing values of exophthalmos (r = 0.553; 0.643; 0.687), but this increase was not statistically significant. This trend was not found for the LRM. When comparing the two time periods (2007-2009 and 2010-2012) during which the study was performed, significantly higher correlations were found for the MRM (P < 0.0001) and LRM (P = 0.0008) in the time period 2010-2012 compared to the time period 2007-2009. Correlation coefficients for the MRM and LRM in the time period 2007-2009 were r = 0.530 and r = 0.426, respectively. In the time period 2010-2012, the correlation coefficients were r = 0.878 for the MRM and r = 0.751 for the LRM. For details, see Table 3.

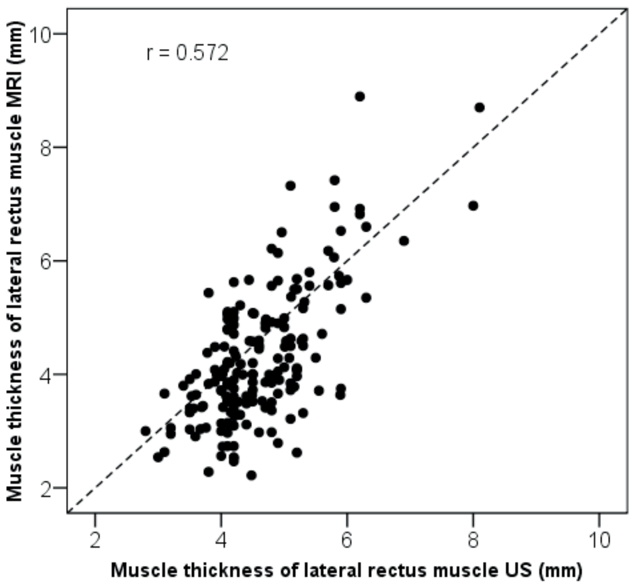

Fig. 2. Spearman correlation between ultrasound (US) and MRI for the lateral rectus muscle (r = correlation coefficient).

DISCUSSION

Enlargement of extraocular muscles is a key sign of TAO. In the initial active phase of TAO, the muscle size increases especially due to muscle inflammation and edema; in the burn-out and inactive phase due to postinflammatory fibrotic changes. TAO is characterized by a spindle-like spread of the recti muscles without involvement of the tendon. The most frequently affected muscles are the medial and inferior recti. Accurate measurement of extraocular muscles is very important for the diagnostic work-up and the follow-up in the treatment of TAO patients.

Demmer & Kerman compared the maximum transverse diameter of the rectus muscles in normal subjects

Table 1. Eye muscle thickness values obtained by ultrasonic measurement (US) and measurement on MRI scans, all given in mm.

	Mean	(SD)	Median	(Range)
Medial rectus (US)	6.12	(1.13)	6.06	(3.80 – 9.80)
Medial rectus (MRI)	5.52	(1.70)	5.00	(3.08 – 11.20)
Lateral rectus (US)	4.60	(0.83)	4.50	(2.80 – 8.10)
Lateral rectus (MRI)	4.28	(1.19)	4.01	(2.22 – 8.90)

Table 2. Median values of the largest diameter of the medial and lateral rectus muscles obtained by ultrasonic measurement (US) and measurement on MRI scans in different subgroups, all given in mm.

	Medial rectus (US)	Medial rectus (MRI)	Lateral rectus (US)	Lateral rectus (MRI)
Entire study group	6.06	5.00	4.50	4.01
Active stage of TAO	6.06	5.24	4.50	4.15
Inactive stage of TAO	6.05	4.67	4.47	3.89
Hertel values < 18 mm	5.24	4.51	4.20	3.72
Hertel values 18–22 mm	5.68	4.85	4.20	3.92
Hertel values > 22 mm	6.50	5.76	4.90	4.41

Table 3. Spearman correlation coefficients between maximal horizontal muscle diameters obtained by ultrasound and by MRI.

	Number of orbits evaluated	Correlation coefficient for medial rectus muscle	Correlation coefficient for lateral rectus muscle
Entire study group	180	0.690	0.572
Active stage of TAO	98	0.712	0.687
Inactive stage of TAO	82	0.662	0.433
Hertel values < 18 mm	31	0.553	0.552
Hertel values 18-22 mm	63	0.643	0.442
Hertel values > 22 mm	86	0.687	0.561
Time period 2007-2009	92	0.530	0.426
Time period 2010-2012	88	0.878	0.751

measured by standardized ultrasound and by high resolution MRI in 39 orbits[27]. They found that the average value for each rectus muscle was similar using these two techniques, but there was larger variability in the ultrasound than in the MRI measurements. This could be explained by several different factors. The value of maximal muscle width is dependent on the angle of incidence of the ultrasound beam which is not always perfectly perpendicular to the muscle surface due to variations in orbital anatomy. Furthermore, extraocular muscles are oval shaped and not round[16,28]. In TAO, US evaluation of extraocular muscles can be even more difficult. Vlainich et al. found poor correlation between US and MRI in the median thickness of recti muscles in 19 patients with TAO (ref.[25]). They found positive correlation only for the medial rectus muscle in the left eye. Lennerstrand et al. examined 32 patients in different stages of TAO and found poor correlation between muscle volume in MRI and muscle thickness in US (ref.[24]). Nagy et al. performed US and MRI examination in 43 patients with diplopia and TAO and found no correlation between the diameters of extraocular muscles[26]. In all these studies, all four extraocular muscles were examined.

In the present study, we found a correlation between maximal horizontal muscle diameters obtained by B-scan ultrasound and by MRI. However, there was a trend to overestimate the muscle width on ultrasound. On the other hand, for markedly enlarged muscle, the US values were underscored compared to MRI (Fig. 1 and 2). The main reason for this is that MRI also enables us to find the thickest section of the muscle in the posterior part of the orbit, the most critical area in cases of severe TAO with the risk of optic neuropathy[26]. Ultrasound is more limited in these cases. Examination of the vertical recti muscles was not included for several reasons. It is difficult to distinguish the levator palpebrae and superior rectus. For this reason most researchers measure these structures together as the superior rectus group and larger coefficients of variation can be found not only using US but also on MRI (ref.[29]). US evaluation of the inferior rectus muscle is sometimes more difficult due to the anatomic configuration of the orbits. Furthermore, evaluation of only horizontal extraocular muscle thickness using B-scan techniques is used in routine daily practice[30].

Several investigations US or MRI in TAO patients demonstrated that extraocular muscle thickness increased with increasing disease severity[31] and with increasing proptosis[30,32]. However, Fledelius et al. pointed out that serious orbitopathy occasionally appears with exophthalmometry levels and/or eye muscle thicknesses generally considered to be within the range for normal eyes[30]. Also in the present study, the largest medians of horizontal recti muscles were found in the group with higher exophthalmometry values (Table 2). Probe placement during US examination is very important (the ultrasound beam must be perpendicular to the muscle surface). Thus, variations in anatomy (a big nose, deep orbits or pronounced brow ridges) could hamper the accuracy of the examination. However, we found no significant difference in the correlation coefficients between US and MRI according to the severity of exophthalmos.

Several studies in recent years focused on the contribution of MRI to the detection of disease activity[33-36]. Ultrasonography is also helpful in determination of the clinical phase of TAO (ref.[14,30]). Low echogenicity of extraocular muscles in TAO patients indicates activity of TAO. It is a marker of edema and inflammation[14]. High echogenicity, on the other hand, is a marker of extraocular muscle fibrosis. In these cases, muscle delineation and discernment from adjacent orbital tissue can sometimes be difficult. This practical experience is consistent with our results. In the present study, comparing correlation coefficients in the active and inactive phases of TAO, higher correlation was found in the active phase of TAO, although a statistically significant increase was found only for the lateral rectus muscle.

As there is low interobserver reproducibility in the case of US (ref.[14]), only one examiner was responsible for all US measurements in the present study. All MRI scans of the orbits were performed in close succession to US. However, the MRI measurements of extraocular muscles for the purpose of this study were performed after the completion of patient enrollments by only one examiner over three weeks. This study design allowed us to ensure homogeneity regarding the technique and reproducibility of the MRI measurements and, on the other hand, monitoring of the US examiner in time flow. Significantly higher correlation was found for both the medial and lateral muscles for the time period 2010-2012 compared to that of 2007–2009. These results confirm that US examination was strongly dependent on the experience of the examiner. We suggest that the main causes of this positive correlation are the design of the study, evaluation of the horizontal recti muscles only, a larger cohort of patients than in previous studies, and, in particular, only one examiner for all US and one for all MRI measurements.

Both ultrasound and MRI are widely used for the detection and follow-up of muscle involvement in patients with TAO. They certainly cannot replace each other. From our clinical point of view, ultrasound B-scan based measurement of the two horizontal rectus muscles is a relatively quick and cheap examination and in connection with clinical ophthalmic examination provides enough information to establish the correct diagnosis. In the hands of an experienced examiner, it is also an important tool for follow-up during the treatment of TAO. US examination of vertical rectus muscles is also possible but larger variability in the results is expected. MRI (or CT) is only occasionally required, especially in cases when imaging of the orbital apex is needed.

CONCLUSION

The B-scan ultrasonographic measurement of horizontal eye muscles thickness in TAO moderately correlates with values obtained using MRI. It proves to be useful for routine clinical practice. Our results have shown that the accuracy of ultrasonographic measurements significantly increases with the experience of the investigator.

ABBREVIATIONS

US, Ultrasound; MRI, Magnetic resonance imaging; TAO, Thyroid-associated orbitopathy; CAS, Clinical Activity Score; MRM, Medial rectus muscle; LRM, Lateral rectus muscle.

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Author contributions: MK, MS: literature search; MK: manuscript writing; MK, JR, MH: study design; MK, RK: data collection; MK, MS: data analysis; MK, MH: data interpretation; JZ: statistical analysis, figures; MK, JR, MH: final approval.

Conflict of interest statement: None declared.

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